REMARKS

The specification has been amended to conform with amendments made in the parent application. Claims 11-16 have been added to claim a method for treating an autoimmune disease which was correspond to claim 11 of the parent application which was subject to a restriction requirement.

The SEQ ID NO:10 on page 5, line 21 is being corrected to conform to Goetinks et al. from which the sequence was taken.

The substitute Sequence Listing is identical to that filed on March 10, 2000 by certified mail in parent Application Serial No. 09/981,340. The substitute Sequence Listing does not contain any new matter and its entry is requested.

RESPECTFULLY SUBMITTED,					
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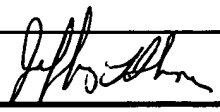
SIGNATURE			DATE	November 13, 2001	
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Attachment: Marked-up copy of amendments.

Marked-Up Copy of Amended Specification - paragraph at page 4, line 32 - page 5, line 10

Although articular cartilage proteins are considered to be the target autoantigens competent of stimulating autoaggressive T cells involved in the destruction of articular cartilage in autoimmune diseases, it was not [untill] until the present invention that these MHC Class II binding T-cell epitopes associated with cartilage-responsive autoreactive T cells have been identified on the cartilage proteins, in particular on HAG and HCLP. The peptides according to the invention resemble these MHC Class II binding T-cell epitopes, thus providing T-cell reactive peptides which can be used in the peptide-induced T cell tolerance therapy. Accordingly, patients can be treated with the peptides according to the invention to induce specific T-cell tolerance not only to the administered peptides but to the target autoantigens HAG and HCLP as [wel] well. As other components of the immune system are not affected by the peptides according to the invention, the immune system of the patient will remain intact and will be able to protect the patient against other infections.

Marked-Up Copy of Amended Specification - paragraph at page 5, lines 15-32

Peptides according to the invention have been described. Perin et al., FEBS Letters 206:73 (1986) describes the structural relationship between link proteins and proteoglycan monomers and discloses a peptide fragment obtained after tryptic digestion of the link protein. The peptide fragment has the amino acid sequence SSAGWLADRSVRYPISKARPNXGG. Goetinck et al., J. Cell Biol. 105:2403-2408 (1987) discloses the peptides NAGWLSDGSVQYPITKPREP and [DAGWLADGHSVRYPISRPRKR] DAGWLADGSVRYPISRPRKR which correspond to the amino acid residues Asn^{207}- Pro^{226} and Asp^{306}-Arg^{325} respectively of the primary structure of link protein. Said peptides were synthesized to study the interactions between link protein and hyaluronic acid and said amino acid residues were found to be involved in the binding of link protein to hyaluronic acid. Neame et al., J. Biol. Chem. 261(8):3519-3535, (1986) describes the elucidation of the primary structure of link protein from rat chondrosarcoma proteglycan aggragate. Analysis

of a triptic digest of the link protein revealed a fragment having the amino acid sequence GGLDWCNAGWLSDGSVQYPITKPR. Perides et al., J. Biol. Chem. Vol. 264, no. 10:5981-5987 (1989) describes the isolation and partial characterization of a glial hyaluronate-binding protein (GHBP). Tryptic digestion of GHBP results in several peptide fragments, one of which having the amino acid sequence EQLFAAYEDGFEQCDAGWLADQTVRYPIRAPRVGCY.

Marked-Up Copy of Amended Specification - paragraph at page 6, lines 14-22

The peptides according to the invention can also be prepared by recombinant DNA techniques. A nucleic acid sequence coding for a peptide according to the invention or a multimer of said peptides is inserted into an expression vector. Suitable expression vectors are, amongst others, plasmids, cosmids, [virusses] <u>viruses</u> and YAC's (Yeast Artificial Chromosomes) which comprise the necessary control regions for replication and expression. The expression vector can be brought to expression in a host cell. Suitable host cells are, for instance, bacteria, yeast cells, and mammalian cells. Such techniques are well known in the art, see for instance Sambrooke et al., Molecular Cloning: a Laboratory Manual, Cold Spring Harbor [laboratory] <u>Laboratory</u> Press, Cold Spring Harbor, 1989.

Marked-Up Copy of Amended Specification - paragraph at page 6, lines 24 to page 7, line 2

According to the invention, patients suffering from T-cell mediated destruction of the articular cartilage can be treated with a therapeutical composition [comprizing] <u>comprising</u> one or more peptides according to the invention and a pharmaceutical acceptable carrier. Administration of the pharmaceutical composition according to the invention will induce tolerance of the specific autoreactive T cells of these patients to the autoantigenic proteins in the articular cartilage under attack and other self antigens which display the identified MHC Class II binding T cell epitopes characterized by one of the amino acid sequences of SEQ ID NO:1-6. More specifically, administration of the pharmaceutical composition according to the invention will induce tolerance

of the specific autoaggressive T cells to the autoantigens HAG [end] and HCLP. The induced tolerance thus will lead to a reduction of the local inflammatory response in the articular cartilage under attack.

Marked-Up Copy of Amended Specification - paragraph at page 12, lines 1-14

PBMC obtained from heparinized venous peripheral blood were isolated by standard centrifugation on a Ficoll-Paque gradient. Cells were cultured in three- or four-fold at a concentration of 1,5 x 10^5 cells/well in DMEM/Ham's F12 medium supplemented with 10% heat-inactivated pooled human serum, L-glutamine, 2-ME and antibiotics in flatbottomed microtiter plates. Cells were incubated in medium alone or in the presence of PHA (2.5 µg/ml) or in the presence of antigens, including the chicken proteoglycan fraction, the chicken collagen fraction, sonicated *Mycobacteriium tuberculosis* or the peptides HAG1, HAG2, HAG3 and HCLP1 in concentrations of 50 µg/ml, 5 µg/ml or 0.5 µg/ml. Cultures were incubated in a total volume of 210 µl for 4, 5, 6 or 7 days at 37°C in a humidified atmosphere of 5% CO_2. Cultures were pulsed with 0.5 µCi (1.85 x 10^4 Bq) [^{3}H]Thymidine ([^{3}H]TdR) for the last 18 hours of cell culture. Cells were harvested on glassfibre filters and [[3H]TdR] [^{3}H]TdR incorporatiopn incorporation was measured by gasscintilation. Note that counting by gasscintilation is fivefold less efficient compared to liquid scintilation. [Therfor] Therefore, filters were measured for 5 min (Packard Matrix 96 β-counter, Meriden CT).